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Painless and Tissue-Saving Injection of Medicaments

The present invention relates to the use of colloid-osmotically effective substances in the infusion or injection of medicaments into vessels of the human or animal body, a kit comprising the individual components, and injectable medicinal solutions.

The injection of medicaments into blood vessels of the body is a frequently used route of administration for medicinal substances. As a rule, a certain amount of the medicinal substance in an aqueous solution or as an emulsion is injected into a small vein extending under the skin. However, with many medicinal substances, tissue damage and/or pain occur immediately after the injection in the area of the vessel into which the medicinal substance has been injected. A first possible cause thereof is the higher concentration of the damaging medicinal substances in the area of the injection site. In addition, the injection of the medicinal substances is often effected with a high hydrostatic pressure. The damage is caused by a contact of the tissue of the vascular wall and of the surrounding connective tissue with the medicinal substances, which are damaging in a higher concentration. Very frequently, medicinal substances in aqueous solutions are adjusted to non-physiological pH values for reasons of stability. After the injection, the tissue of the vascular wall and the surrounding connective tissue are damaged by diffusing protons or hydroxide ions (depending on the titration acidity of the adjusted buffer solutions). Thus, for example, it is known that the inadvertent intra-arterial injection of the narcotic thiopental may lead to massive necroses in the course of the arterial vessel up to loss of the extremity.

According to the prior art, this damage is counteracted by various methods and means. Most frequently, it is attempted to prevent damage by diluting the injected

medicinal substances, either by introducing them into a current infusion, or by mixing with an infusion solution prior to infusion. It is a common feature of all dilution methods that a relatively small quantity of the medicinal substance is mixed with a larger volume of an infusion solution. The drawbacks of these dilution methods reside in the larger volume of liquid which is loaded on the patients, who may suffer from a circulatory disturbance, for example, and in the resulting time for application which is too long for many pharmaceutically active substances. Frequently, a bolus is desired, i.e., injection of a small volume with concentrated medicinal substance within a short period of time, i.e., within a few minutes or seconds.

By infusion into vascular catheters lying in larger vessels (e.g., central vein catheters), potentially damaging medicinal substances can be diluted by the patient's blood after injection. A precondition thereof is the installation of a central vein catheter with all accompanying risks (false puncture, bacterial colonization of the catheter and complicating bacteriaemia) and costs. Another method consists in infusing medicinal substances, not in aqueous solutions, but as an emulsion with fats. However, in this case too, damage and pain occur after the injection of the medicinal substances due to passage of the medicinal substances into the vascular wall and the connective tissue.

To date, colloid-osmotically effective macromolecules, such as hydroxyethylstarch, dextranes and other polysaccharides or polypeptides, such as polygelatin or albumin, have been employed as components of blood and plasma substitute solutions (volume substitutes, plasma expanders). In this case, they serve as a substitute of the colloid-osmotical effect of the endogenous plasma proteins and are therefore infused in hemodynamically relevant amounts, i.e., several grams per day. The infusion volume of such hemodynamically effective solutions is within a range of several hundred milliliters.

Thus, US-A-5,434,191 describes an artificial blood in the form of an aqueous emulsion comprising water, an emulsifier, a synthetic phospholipid, a perfluorinated compound as an oxygen carrier, and a compound selected from the group consisting of hydroxyethylstarch, polyvinylpyrrolidone, modified gelatin, dextrane

or some similar substance which provides for a colloid-osmotic pressure. However, due to the renal complications associated with artificial blood, this system has not yet become established as a blood substitute.

EP-A-0 650 736 describes the use of recombinant human serum albumin (rHSA) for increasing the blood plasma quantity, for supplementing the circulating blood volume, for improving hypoproteinemia, and for maintaining the colloid-osmotic pressure.

As with electrolyte solutions, e.g., physiological salines, some colloidal plasma substitute solutions may also be used as a carrier solution for medicaments. Thus, a medicament is injected into the infusion solution during the infusion and thus diluted in some hundred milliliters of the solution (Rote Liste 1997, Editio Cantor Verlag, No. 52275, Haemaccel). In principle, infusion of such substances causes a permanent increase of the colloid-osmotic pressure in the blood. In order to ensure this effect for a sufficient long period of time, all hemodynamically effective plasma substitutes have a half-life within a range of up to a few hours. All these colloid-osmotically effective macromolecules which exhibit prolonged dwelling times in the blood are first taken up by cells of the reticuloendothelial system and stored depending on the kind of substance.

In a particular application, colloids are used for expanding the interstitial space. Thus, US-A-5,424,288 describes a method for the treatment of tumor cancer in organisms by administering a suspension of macro-aggregated albumin in an inert fluid into the tumor, followed by the injection of a colloidal radioactive agent.

In the Journal of Biological Response Modifiers (1985), 4/4 (340-352), V. Bocci describes a method for increasing the interstitial connective tissue space for subcutaneously or intramuscularly administered medicinal substances, which then arrive in the lymph tracts.

It has been the object of the invention to enable medicaments to be administered into vessels of the human or animal body by appropriate measures in such a way that vascular damage, especially local vascular damage, of the perivascular

connective tissue is highly reduced and, in the ideal case, completely suppressed, and/or that the pain associated with the administration occurs only in a reduced form and, in the ideal case, is completely suppressed. Thus, by appropriate measures, these side-effects on the injection vessel which depend on the concentration of the medicinal substance are to be counteracted. "Injection vessel" as used herein means the vessel (vein, artery etc.) into which the medicinal composition is administered and which communicates with other vessels. Further, it has been the object of the present invention to provide an injectable aqueous medicinal solution (medicament), especially as a ready medicament or as a kit.

The object of the invention was achieved by the use of colloid-osmotically effective substances for preparing an injectable aqueous solution of at least one pharmaceutically active ingredient for its painless and/or tissue-saving introduction into vessels of the human or animal body.

Often, the vascular damage is associated with pain-causing irritations of the perivascular connective tissue so that vascular damage, especially local vascular damage, and pain-causing irritations of the perivascular connective tissue can be reduced and, in the ideal case, completely avoided according to the invention.

The principle according to the invention prevents vasculitis, i.e., an inflammatory response which starts from the wall of the vessels, especially the blood vessels, of the human or animal body.

According to the invention, the diffusion of the pharmaceutically active component through the vascular walls of the injection vessel and the accompanying local vascular damage as well as the pain-causing irritations of the perivascular connective tissue, which may additionally occur, are clearly reduced, preferably completely prevented.

According to the invention, the colloid-osmotically effective substances are natural or synthetic colloid-forming macromolecules which have a colloid-osmotic pressure in aqueous solution of > 1333 Pa (10 mm Hg), preferably > 3733 Pa (28 mm Hg, corresponding to the colloid-osmotic pressure of plasma).

The colloid-forming macromolecules are selected from the group consisting of polysaccharides, modified polysaccharides, polypeptides, modified polypeptides, and proteins, such as albumins.

The polysaccharides are preferably cellulose, starch or dextrane, hydroxyethylstarch [poly(O-hydroxyethyl)starch] being preferred as a polysaccharide. According to the invention, those hydroxyethylstarches may be used, in particular, which have a degree of substitution, DS, of < 0.4. The degree of substitution, DS, is defined as the proportion of substituted anhydroglucose units among all anhydroglucose units. It can be determined from the measured amount of unsubstituted glucose after hydrolysis of a sample. Preferably, the degree of substitution, DS, is at least 0.10, more preferably at least 0.15.

The hydroxyethylstarches employed according to the invention preferably have an average molecular weight of below 300,000, preferably of below 70,000, and even more preferably of below 40,000. More preferably, the hydroxyethylstarch has a degree of substitution, DS, of between 0.1 and < 0.4 and an average molecular weight of below 300,000.

Another polysaccharide which can be employed as a colloid-osmotically effective substance according to the invention is dextrane, preferably having an average molecular weight of below 40,000, more preferably of below 20,000, and even more preferably of below 15,000.

The polypeptides and modified polypeptides employed as colloid-osmotically effective macromolecules according to the invention are selected from the group consisting of gelatin, oxypolygelatin, gelatin succinate. The oxypolygelatin and the gelatin succinate preferably have an average molecular weight of below 40,000, preferably of below 20,000. The proteins are preferably albumin, human albumin, cleavage products of albumin, or recombinant human serum albumin (rHSA).

In contrast to colloids employed as plasma expanders, a sustained effect on the colloid-osmotic pressure in the blood or a prolonged dwelling in the blood as an additional pharmacological effect is not desired according to the invention. For the

effect intended according to the invention, it is only necessary for the colloids to remain within the vascular system of the injection vessel and to have a transient colloid-osmotic effect. Ideally, the substances are excreted from the body already during the first passage through the kidneys. It is known that the serum half-life of the hydroxyethylstarch primarily depends on its degree of substitution, DS. Its molecular weight plays a rather inferior role. However, for the water-solubility of the starch, a minimum amount of hydroxyethyl groups is necessary. A low-substitution hydroxyethylstarch having a degree of substitution of below 0.4, for example, having an average degree of substitution of 0.3, would have a satisfactory colloid-osmotic effect in the infusion vessel for sufficiently high molecular weights, but would be excreted (e.g., renally eliminated) from the body very quickly after the infusion. Due to its quick elimination, this hydroxyethylstarch would be hardly useful as a plasma expander. A relevant load on the reticuloendothelial system or a cumulative storage in organs would not occur even upon repeated injections.

For the other colloidal plasma expanders mentioned above, there is a pharmacokinetic relationship between the molecular weight and the serum half-life. Accordingly, for dextranes having an average molecular weight of below 40,000, preferably below 20,000, a correspondingly quicker elimination from the body can be observed. Also with oxypolygelatin or gelatin succinate, a quick elimination from the body can be caused by an average molecular weight of below 40,000, preferably below 20,000, more preferably below 15,000. A substantial increase of the colloid-osmotic pressure in the patient's blood cannot be induced permanently even by quantitatively larger infusions of such solutions having lower average molecular weights.

Independently of pharmacokinetics, the application of a colloid-osmotically effective principle means an injection of low quantities of colloidal macromolecules. A volume of 10 ml of a claimed injection solution having a colloid concentration of 10% contains 1 g of colloid, whereas the injection of medicaments into colloidal plasma substitute solutions (plasma expanders) as carrier solutions causes a colloid load of 50 g, a significant increase of the colloid-osmotic pressure in the

patient's blood, and a frequently undesirable dilution or too slow an administration of the medicinal substance.

The proportion of the colloid-osmotically effective substance is from 2 to 25% by weight, preferably from 3 to 15% by weight, based on the total amount of the injectable aqueous solution.

The injectable aqueous solutions of medicinal substances employed according to the invention have an osmolarity of between 250 and 400 mOsmol/l, preferably between 300 and 350 mOsmol/l. The tonicity of the solution to be injected can be adjusted by an additional cation proportion of from 100 to 170 mmol/l, preferably from 100 to 150 mmol/l, and an anion proportion of from 100 to 170 mmol/l, preferably from 100 to 150 mmol/l. Part of the cation and/or anion concentration can be replaced by a natural or synthetic polyol. Polyols suitable for this purpose are known in the prior art. In an illustrative way, there may be mentioned sugars, such as glucose, and synthetic polyols, such as sorbitol or xylitol.

The pH value of the solution employed is essentially determined by the requirements in terms of the stability in aqueous solution of the medicinal substance to be administered. The pH value may be between 1.5 and 12, preferably between 4.5 and 8. The solutions used according to the invention are free of particles and free of emulsion-forming perfluorinated organic compounds. Thus, the compositions used according to the invention are neither emulsions nor suspensions. The injectable compositions may further contain additives and auxiliaries which are common in infusion therapy and physiologically acceptable, such as buffer systems. As a buffer, the amino acid histidine, preferably in a dosage of from 50 to 150 mmol/l, and histidine hydrochloride, preferably in a dosage of from 5 to 20 mmol/l, may be added to the solution.

According to the invention, medicinal substances can be employed as the pharmaceutically active ingredient which are selected from the group consisting of slimming preparations/anorexiants, acidose therapeutics, amino acids (e.g., histidine) or modified amino acids, analeptics/antihypoxemics, analgetics/antirheumatics, anthelmintics, antiallergics, antianemics, antiarrhythmics, antibiotics/

antiinfectives, antidementives (nootropics), antidiabetics, antidotes, antiemetics/ antivertiginosics, antiepileptics, antihemorrhagics (antifibrinolytics and other hemostatics), antihypertensives, antihypoglycemics, antihypotensives, anticoagulants, antimycotics, antiparasitics (internal), antiphlogistics, antitussives/expectorants, anti-arteriosclerosis agents, balneotherapeutics and agents for heat therapy, beta receptor and calcium channel blockers and inhibitors of the renin-angiotensin system, broncholytics/antiasthmatics, cholagogics and bile duct therapeutics, cholinergics, corticoids (internal), dermatics (internal), dietetics/ nutrition therapeutics, diagnostics and agents for diagnostic preliminaries, diuretics, agents stimulating blood flow, withdrawal agents, enzyme inhibitors, enzyme preparations and transport proteins, fibrinolytics, geriatric agents, gout agents, influenza remedies, gynecologic agents, anti-hemorrhoidal agents (proctologics), hepatics, hypnotics/sedatives, hypophysis and hypothalamus hormones, regulatory peptides and their inhibitors, immunotherapeutics and cytokines, infusion and standard injection solutions, organ perfusion solutions, cardiacs, anti-caries and anti-parodontosis agents and other dental preparations, coronary agents, laxants, lipid depressants, neural therapeutics, gastro-intestinal agents, migraine remedies, mineral preparations, muscle relaxants, narcotics, parathyroid hormones/calcium-metabolic regulators/osteoporosis remedies, neuropathy preparations and other neurotropic agents, neurotransmitters (e.g., dopamine) or modified neurotransmitters, ophthalmics, otologics, Parkinson remedies and other remedies against extrapyramidal disturbances, psychopharmacons, sinusitis remedies, roborants/ tonics, thyroid therapeutics, serums, immunoglobulins and vaccines, sexual hormones and their inhibitors, spasmolytics, platelet aggregation inhibitors, tuberculosis remedies, alterants, urologic agents, vein therapeutics, vitamins, wound treatment agents, cytostatics and metastasis inhibitors. The pharmaceutically active ingredient may be contained in the injectable solution in a proportion of from 0.5 to 25% by weight, preferably from 2 to 15% by weight, more preferably from 5 to 10% by weight, based on the total amount of the injectable solution.

The aqueous medicinal solutions used according to the invention can be favorably affected by the colloids employed in terms of water-solubility, stability, rheological properties and viscosity. Similarly, advantageous changes in terms of electric conductivity, filtration properties, temperature conductance, acoustic resonance,

chemoluminescence and phagocytability are possible by appropriately selecting the colloid-osmotically effective substance.

The invention further relates to a kit comprising the components of the composition used according to the invention in a separated form. In detail, the kit comprises the colloid-osmotically effective substance in an aqueous solution and, separately, the medicinal substance in a solid, liquid or dissolved form. For the colloid-osmotically effective substance and the pharmaceutically active substances, reference is made to the above statements. Prior to application (injection, infusion), the two components are mixed and administered using a perfusor and/or infusion machine, which may also be independently contained in the kit. The perfusor or the infusion machine may be controlled by a processor which receives signals from a measuring device or input appliance. For the properties and the other components which may be contained in the aqueous injectable solution, reference is made to the above statements.

In another particular embodiment, the invention relates to an injectable aqueous medicinal solution comprising at least one pharmaceutically active ingredient selected from the group described above, and a colloid-osmotically effective substance selected from the group described above, especially from the group consisting of polysaccharides, modified polysaccharides and gelatin. The polysaccharides and modified polysaccharides are selected from the group consisting of starch and modified starch. However, it is particularly preferred to use the hydroxyethylstarch described in more detail above in the way described in detail above.

In the form of their ready medicament, the above described injectable aqueous medicinal solutions are suitable for injecting medicinal substances which, if injected in another form, would lead to tissue damage and/or pain.

The preparation of the injectable aqueous medicinal solution can be effected according to known methods of the prior art, especially by mixing the individual components to form the solution. For preparing the kit, the individual components are filled in suitable containers, sealed and provided separately in the form of the

kit until use. According to the invention, pharmaceutically active substances can be injected quickly and in high concentrations while the vascular damage, especially local vascular damage, at the site of injection is reduced, and usually even completely suppressed. Due to the reduction of the irritations of the perivascular connective tissue, hardly any pain, or none at all, occurs at the site of injection.

Particularly advantageous is the possibility to administer small boluses, especially injection boluses of up to 20 ml, preferably up to 10 ml, more preferably up to 5 ml, or infusion boluses of up to 100 ml, preferably up to 50 ml.

Example

In a 10% by weight aqueous solution of hydroxyethylstarch (DS < 0.4; average molecular weight < 70,000), 20 mg of etomidate was dissolved in the presence of 100 mmol/l of anion proportion and 100 mmol/l of cation proportion, and quickly injected intravenously. The injection proceeded without pain.